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Cystic Fibrosis and Calcium Oxalate Nephrolithiasis

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During the past six years. we have treated eight patients with cystic fibrosis (CF) for nephrolithiasis. In seven patients, the stones were comprised of calcium oxalate. Another six patients had calcium oxalate crystalluria. In our CF population of 140 patients, this represents a cumulative incidence of calcium oxalate nephrolithiasis of 5.7 percent and an additional 4.2 percent incidence of crystalluria. Experience with these patients is reviewed. Pancreatic insufficiency was universally associated with nephrolithiasis or crystalluria. Diabetes and cirrhosis were also common. Predisposing factors and potential mechanisms of stone disease in pancreatic insufficient CF patients are discussed, focusing on the relationship between fat malabsorption in CF to oxalate metabolism.

INTRODUCTION

Nephrolithiasis is a relatively uncommon clinical problem in pediatric and young adult patients with an incidence varying regionally in the United States between one in 1000 in the south and one in 7000 in the northern states [1]. Kidney stones are associated with various pathologic states [2], and their formation is closely related to renal calcium handling and to the concentration of substances with stone-forming activity in the urine [3]. Nephrolithiasis causes a classic triad of findings including hematuria, dysuria and flank pain, but in younger patients the presentation of nephrolithiasis may be variable [4]. Cystic fibrosis (CF)[b] is a multi-system genetic disease characterized by abnormal epithelial electrolyte transport. Two of the major manifestations of CF include chronic suppurative lung disease and exocrine pancreatic insufficiency that causes intestinal fat malabsorption. The CF-gene product, cystic fibrosis transmembrane conductance regulator (CFTR) is thought to be a cAMP-dependent chloride channel and is located in many organs, including the kidney [5]. Although its role there is unknown, and no baseline renal abnormality is defined [6], CF and its therapy is associated with several urinary abnormalities. These include hypercalciuria [7, 8], hyperuricosuria [9, 10] and microscopic nephrocalcinosis [8]. Despite this, reports of nephrolithiasis in CF patients are uncommon [11-13].

We report our experience caring for eight patients with CF and nephrolithiasis at our CF center over the past six years. In seven of the eight patients, stone analysis revealed the composition to be calcium oxalate. An additional six patients had calcium oxalate crystalluria. The paucity of information about this association led us to review our experience with CF and calcium oxalate nephrolithiasis focusing on the gastrointestinal manifestations of CF, which may predispose these patients to this condition. In addition, we review

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[b]*Abbreviations:* CF, Cystic Fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

our therapeutic experience with these patients and pose several questions related to future research.

SUBJECTS AND METHODS

Patients with CF followed at the Yale-New Haven Hospital CF Center are included in this analysis. The study encompasses a six-year period during which all of the renal stones were diagnosed. The diagnosis of CF was confirmed by sweat chloride analysis in accordance with the standards of the North American Cystic Fibrosis Foundation. All stones were documented either radiographically, with intravenous pyelogram, ultrasonography or abdominal radiograph, or by roentgenographic diffraction stone analysis. Crystalluria and hematuria were diagnosed by microscopic examination of urine specimens. Three patients undertook 24-hour urine collections for oxalate while eating a regular diet. Serum carotene level, an indirect measure of fat malabsorption, is available for four patients.

The inpatient and outpatient medical record of each patient with calcium oxalate nephrolithiasis or crystalluria was reviewed retrospectively with regard to age, sex, family history, recurrence of stone disease, medications, end-organ complications of CF and the clinical presence or absence of pancreatic insufficiency based on growth parameters, stool characteristics and the need for pancreatic enzyme supplementation.

RESULTS

Patient characteristics are noted in Tables 1-3. The cumulative incidence of nephrolithiasis at this CF center of approximately 140 patients was 5.7 percent, and an additional 4.2 percent of patients had oxalate crystalluria. Salient features of the patients with stones included an average age of 23 years (range 15 to 34 years), a male-to-female ratio of 0.6:1, a 38 percent incidence of diabetes and a 25 percent incidence of cirrhosis. Seven of the patients with nephrolithiasis presented with renal colic, and the other patient developed pancreatic insufficiency and stone disease after a bout of acute pancreatitis.

Patients with crystalluria also had an average age of 23 years (range five to 33 years), a male-to-female ratio of 2:1, a 33 percent incidence of diabetes and a 16 percent incidence of cirrhosis.

All of the patients in both groups were pancreatic insufficient on clinical grounds, and serum carotene levels were abnormally low in one patient with nephrolithiasis and in two patients with crystalluria. Serum carotene level was normal in one additional patient with crystalluria. One patient with nephrolithiasis and allergic bronchopulmonary

Table 1. Patient characteristics.

Patients with nephrolithiasis (n = 8):

- Age: 15 to 34 years (mean 23 years)
- Three male, five female
- Cirrhosis: 2/8
- Diabetes: 3/8
- Renal colic: 7/8

Patients with crystalluria (n = 6):

- Age: 5 to 33 years (mean 23 years)
- Four male, two female
- Cirrhosis: 1/6
- Diabetes: 2/6
- Hematuria: 4/6

Table 2. Characteristics of patients with nephrolithiasis.

Age (yrs)	Sex	Urine oxalate[a]	Stone analysis	Imaging study
20	F	56 mg/24 hrs	CaOXALATE[b]	IVP[c]
15	M	53 mg/24 hrs	No	NA[d]
19	F	NA	No	IVP
25	F	NA	CaOXALATE	RUS[e]
20	F	NA	CaOXALATE	NA
34	M	NA	CaOXALATE	NA
17[g]	F	81 mg/24 hrs	No	KUB[f]
32[h]	M	NA	No	IVP

a: Normal value for urine oxalate, <40 mg/24 hours; *b*: CaOXALATE, calcium oxalate; *c*: IVP, intravenous pyelogram; *d*: NA, not available; *e*: RUS, renal ultrasound; *f*: KUB, radiograph of kidneys, ureters and bladder; *g*: Serum carotene level in this patient, 28 ug/dl (0.52 umol/l) (normal value, 70-200 ug/dl, 1.12-3.72 umol/l); *h*: The etiology of stone disease in this patient is undiagnosed.

Table 3. Characteristics of patients with crystalluria.

Age (yrs)	Sex	Hematuria	Carotene[a] (ug/dl)
29	M	+	26 (0.48 umol/l)
33	M	+	53 (0.98 umol/l)
24	F	+	103 (1.91 umol/l)
5	M	-	NA[b]
16	F	-	NA
33	M	+	NA

a: Normal value for serum carotene, 70-200 ug/dl, 1.12.-3.72 umol/l; *b*: NA, not available.

aspergillosis, and one patient with crystalluria and severe reactive airways disease were treated with chronic, oral corticosteroid therapy. No patient received diuretics, and of the patients with nephrolithiasis and crystalluria, two in each group never received intravenous aminoglycosides.

No patient was ill enough to have severe activity limitation, and no bony fractures occurred in these patients. The spectrum of pulmonary involvement varied. Only one patient has had recurrent renal colic, and no renal impairment was noted. Family history of nephrolithiasis was negative in all cases. Genetic analysis of these patients was unavailable.

DISCUSSION

This series of patients with CF and calcium oxalate nephrolithiasis or crystalluria strongly supports evidence of an association between these two conditions. The universal association between fat malabsorption due to pancreatic insufficiency and oxalate nephrolithiasis may provide an important mechanistic clue regarding the pathogenesis of stone disease in CF. Enteric hyperoxaluria with nephrolithiasis is well described in

patients with gastrointestinal disorders, and in particular, malabsorption of fat [14]. The mechanism of enteric hyperoxaluria is well characterized [15-18].

In enteric hyperoxaluria, excess free fatty acids in the gastro-intestinal tract complex with dietary calcium to form insoluble soaps. This pool of dietary calcium is rendered unavailable to bind with dietary oxalate. (Calcium oxalate is a highly insoluble salt, responsible for fecal excretion of most dietary oxalate.) Oxalate, which is unbound to calcium complexes with other cations, such as sodium, forms soluble salts that are readily absorbed. The pool of passively absorbed oxalate is expanded, increasing the filterable load of oxalate on the nephron. In the proper biochemical milieu, supersaturation of the urine with calcium and oxalate can occur, followed by crystallization, and possibly stone formation.

In enteric hyperoxaluria, the degree of fat malabsorption has been directly correlated with oxalate hyperabsorption and hyperoxaluria [15]. In fact, many patients with enteric hyperoxaluria have recurrent stone disease and acute renal injury has been reported [19]. Pancreatic insufficiency with dietary fat malabsorption commonly occurs in CF despite pancreatic enzyme replacement therapy. In addition, the disruption of entero-hepatic circulation of bile salts is also known to occur in CF [20] and can also lead to oxalate hyperabsorption by the following mechanism. With decreased absorption of bile salts, the bile salt load on the colon increases, causing exaggerated mucosal permeability and colonic hyperabsorption of oxalate [21-23]. We believe that these factors are likely to be closely related to the oxalate nephrolithiasis and crystalluria demonstrated by these patients.

Treatment of nephrolithiasis has been straightforward, consisting of hydration and analgesia acutely. Chronic therapy includes dietary avoidance of oxalate, minimizing steatorrhea with careful adjustment of pancreatic enzyme therapy, with or without the addition of antacids to maximize the efficacy of the enzyme dose, and ensuring adequate hydration. Recurrent renal colic has been problematic for only one patient, but persistent crystalluria is more common. No evidence of renal damage is apparent.

SUMMARY

Based on this series of patients, we report that calcium oxalate nephrolithiasis is a complication of CF, with an incidence at this CF center of over five percent. Diabetes and cirrhosis were common in our patients, and pancreatic insufficiency with fat malabsorption was universal. Nephrolithiasis likely results from enteric hyperoxaluria associated with pancreatic insufficiency, and the effects of abnormal bile salt metabolism on colonic oxalate absorption. While these phenomena provide a potential pathophysiologic model, metabolic studies of oxalate absorption and metabolism in CF are needed to confirm this observation as is research exploring the role of CFTR in the kidney. The presentation of kidney stones in children and young adults with CF should be recognized by the practitioner and nephrolithiasis included in the differential diagnosis of abdominal pain in the older CF patient.

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